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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

LOEB, BRONWEN

ART UNIT

PAPER NUMBER

1636

DATE MAILED: 03/26/2003

23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/392,682

Applicant(s)

GRUENERT ET AL.

Examiner

Bronwen M. Loeb

Art Unit

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 October 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 17-44 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 17-44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

This action replaces the action mailed 17 December 2002 which inadvertently was a duplicate of the action mailed 3 October 2001. The Office apologizes for the error and any inconvenience it has caused.

Continued Prosecution Application

The request filed on 1 October 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/392,682 is acceptable and a CPA has been established. An action on the CPA follows.

The amendment filed 3 December 2001, which was entered in the case and considered in the Advisory Action mailed 14 December 2001, amended claims 17, 20-30, 35 and 37 and provided new claims 41-44. The following action is in response to the traversals presented in the amendment filed 3 December 2001, and repeats the explanations provided in the Advisory Action mailed 14 December 2001.

Claims 17-44 are pending.

Response to Amendment

1. The rejection of claims 20-36 under 35 U.S.C. §112, second paragraph, as being indefinite has been withdrawn in view of Applicant's amendment filed 3 December 2001.
2. Claims 17, 20-26, and 28-36 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9, 10 and 12 of U.S. Patent No. 6,010,908.

Claims 18, 19 and 38-40, and new claims 43 and 44, stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 17 and 20-36, and new claims 41 and 42, stand rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a method for replacing a target fragment in a cell in vitro, does not reasonably provide enablement for a method of replacing a target fragment in vivo or ex vivo, wherein the cells are intended for gene therapy use. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 17-20, 27-30, 32 and 37-40, and new claims 41-44, stand rejected under 35 U.S.C. §102(e) as being anticipated by Berns et al (USP 5,789,215).

Claims 17-20, 26-29, 31 and 37-40, and new claims 41-44, stand rejected under 35 U.S.C. §102(b) as being anticipated by Vega (Human Genetics (1991) 87:245-253).

Claims 17, 20, 21, 23, 27-30, 32 and 37, and new claims 41 and 42, stand rejected under 35 U.S.C. §102(b) as being anticipated by Shesely et al (Proc. Natl. Acad. Sci. USA (1991) 88:4294-4298).

Claims 17, 18, 20-22, 27-32 and 37-39, and new claims 41-44, stand rejected under 35 U.S.C. §102(e) as being anticipated by Kay et al (USP 5,612,205).

Claim 37 stands rejected under 35 U.S.C. §102(b) as being anticipated by Tsui et al (WO 91/10734).

Claims 17-20, 26-29, 31 and 36-40, and new claims 41-44, stand rejected under 35 U.S.C. §103(a) as being unpatentable over Vega.

Response to Arguments

3. With regard to the rejection of claims 18, 19, 38-40, 43 and 44 under 35 U.S.C. §112, first paragraph, for lack of enablement, and claims 17, 20-36, 41 and 42 under 35 U.S.C. §112, first paragraph, for lack of enablement for full scope of claims, Applicant's arguments have been considered fully but are deemed not persuasive.

The following factors have been considered in formulating these rejections (In re Wands, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are very broad. Claim 17 encompasses the method of replacing a target fragment in a cell, including ex vivo and in vivo embodiments. Claim 18 encompasses the method of claim 17 wherein the cell is ex vivo. Claim 19 encompasses the method of claim 17 wherein the cell is in vivo. Claim 38 encompasses a method for gene therapy wherein a replacement fragment is delivered into a cell and corrects a genetic defect.

The nature of the invention is a method of treatment by replacing a target fragment in a gene associated with a disease with an exogenous replacement fragment which

Art Unit: 1636

corrects the genetic defect in the disease-associated gene. The delivery of nucleic acid in vivo or ex vivo for therapeutic purposes constitutes gene therapy.

An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Vera et al (Nature(1997) 389:239-242) and Palù et al (J. Biotechnol. (1999) 68: 1-13) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. See Verma et al, p. 239, 1st paragraph; Pala et al, p. 1, Abstract. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al indicates that most approaches suffer from poor efficiency and transient expression of the gene (p. 239, col.3, 2nd paragraph). Likewise, Luo et al (Nature Biotechnology (2000) 18:33-37) indicates that non-viral synthetic delivery systems are very inefficient. See p. 33, Abstract and col. 1, 1st and 2nd paragraphs. While all three references indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique. See Verma et al, p. 242, col. 2-3; Pala et al, pp. 10-11; Luo et al, p. 33, col. 1, 1st paragraph.

The relative skill of those in the art of gene therapy and homologous recombination is high.

The area of the invention is unpredictable. As discussed above, the method of in vivo or ex vivo gene therapy is highly complex and unpredictable. Indeed, the recent tragic

Art Unit: 1636

and unexpected death of a participant in a gene therapy clinical trial clearly illustrates the unpredictable nature of gene therapy. See Fox, ASM News, Feb. 2000,66 (2): 1-3.

The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

The present specification provides little or no guidance to support the claimed invention for gene therapy applications. There is no direction provided as to how to overcome the obstacles to gene therapy recognized by leaders in the field, particularly low efficiency of delivery of the nucleic acid. There is no direction on how to ensure that cells from the ex vivo method would replace, or otherwise out-compete, the endogenous defective cells.

There are no working examples disclosed which encompass in vivo or ex vivo applications of the claimed methods.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine how to use the method to treat a condition, one of skill in the art would have to determine how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency and how to obtain a sufficient level of homologous recombination in the target cells to achieve a level which would provide sufficient expression to induce at least some therapeutic effect. If the targeted genetic deletion is a dominant negative, one would have to further determine how to ensure replacement of both copies (assuming a single locus gene) of the defective exon. Since neither the prior art nor the specification provides the answers to

Art Unit: 1636

all of these questions , it would require a [large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to use the claimed method of ex vivo or in vivo gene therapy for replacing a target fragment using homologous recombination.

Applicant argues that the specification is enabling for gene therapy and that the rejection under 35 USC§112, first paragraph should be withdrawn. Applicant is reminded that a disclosure must be enabled at the time of filing. See MPEP §2164.01. Applicant first states that gene therapy is not per se an unpredictable art. This statement is correct in that one cannot predict success for gene therapy methods given the current state of the art, and this is more certainly true at the time of the claimed effective filing date for the instant application. Phase I clinical trials, used to evaluate safety, determine a safe dosage range, and identify side effects for a method or drug, typically enrolls 20-80 patients. Therefore, two or three patients having some success in over 300 clinical trials is an 0.05% "success" rate and clearly predicts a lack of success for gene therapy methods. Applicant cites Ferber (Exhibit B) as further evidence that one of skill in the art has a reasonable expectation of success using Applicant's method for gene therapy. The Examiner disagrees. Ferber, published in 2001, characterizes Applicant's method as a technique which "offer[s] a *potential* means to achieve a

Art Unit: 1636

longtime dream of gene therapy..”(p.1639 box; emphasis added). Indeed, Ferber starts the article with the statement that most nonviral delivery methods “have not been as efficient as viruses in shuttling genes into cells” (p. 1638) and the concluding paragraph of the article states “complex nonviral carriers are a long way from the clinic, but they may offer a glimpse of future gene therapies” (p. 1642). Therefore, one of skill in the art would recognize only that Applicant’s method is considered promising, not that it would be successful.

Applicant states that they have met the legal standard for enablement. Applicant argues that “replacing target gene fragments in even a small percentage of instances” would enable the method. This statement is not correct. While the claims do not explicitly recite a method of gene therapy, the specification does and it is the only use taught for the in vivo method. Gene therapy implies a therapeutic effect. Thus, what needs to be demonstrated for enablement is that the claimed method would achieve a therapeutic effect. Applicant points out the working examples using the method to replace genetic sequences in cell cultures and states that “the Office Action presents no reasoning or evidence to question that these successful modifications demonstrated in vitro are not predictive of successful in vivo modification”. One of skill in the art is well aware that in vitro work cannot be extrapolated to in vivo work. For instance, Applicant’s own article (Exhibit C), published in 2001, states that “one difficulty in going from in vitro to in vivo experiments is that the conditions relevant to transfer (the delivery vehicle, the target and the route of delivery) are different”. (pp.961-962 bridge)

Applicant concludes the argument rebutting the enablement rejections by presenting five post-filing date articles. Only two of these articles present in vivo work, Exhibit C and Exhibit E. These articles were published in 2001 and 1998 respectively. Applicant states that these article demonstrate successful in vivo use of the claimed method follwing the teachings of the specification. The specification generally teaches the use of liposomes as one method for in vivo work. Example 19 is a prophetic in vivo example and refers to Example 17 for the preparation of the replacement DNA fragment and example 15 for the encapsulation. Example 17 does not discuss the preparation of a DNA fragment at all. Example 15 uses DOPE and gramicidin S to prepare liposomes. In contrast, Exhibit C uses four different carriers, none of which consists of DOPE and gramicidin S. Exhibit E uses Lipofectin, which consists of DOTMA. Given that efficiency and sufficiency of delivery is one of the major obstacles to overcome in gene therapy, the delivery vehicle used is critical. None of the three delivery vehicles used in Exhibit C, nor the vehicle used in Exhibit E, were taught or suggested in the instant specification. Thus, these articles do not serve to show the specification was enabled as filed for in vivo methods. The rejections are maintained.

4. With regard to the rejection of claims 17-20, 27-30, 32 and 37-44 under 35 U.S.C. §102(e) as being anticipated by Berns et al (USP 5,789,215), Applicant's arguments have been fully considered but are deemed not persuasive.

Berns et al teaches a method for modifying the genome of an animal cell by delivering a targeting DNA molecule having desired sequence modifications in a

Art Unit: 1636

segment of DNA which is isogonics with the target DNA in the genome to the cell and wherein homologous recombination yields the modified genome. The method may be done ex vivo or in vivo. The delivery methods include electroporation and transfection. The method may be used to correct a defective gene and can target an exon. In example I, their targeting DNA molecule, a double stranded DNA molecule obtained by restriction enzyme cleavage of a plasmid, comprises the 19th and 20th exons of the retinoblastoma gene and adjacent sequence (i.e. intronic sequences). Recombinant cells may be identified by PCR or by Southern hybridization analysis.

Applicant argues that Berns et al teaches the use of a plasmid vector containing two exons of interest and that the plasmid vector constitutes vector sequence. Berns et al teaches targeting exons for replacement by homologous recombination. See col. 9, lines 64-67. Berns also teaches that the targeting DNA may be constructed exclusively from genomic DNA (col. 11, lines 62-63) or synthetically (col. 12, lines 39-42). Such methods would not include vector sequence. The rejection over Berns is extended to new claims 41-44 as Berns et al teaches the use of animal cells, including human cells (see col. 11, lines 31-38).

5. With regard to the rejection of claims 17-20, 26-29, 31 and 37-44 under 35 U.S.C. §102(b) as being anticipated by Vega (Human Genetics (1991) 87:245-253) and the rejection of claims 17-20, 26-29, 31 and 36-44 under 35 U.S.C. §103(a) as being unpatentable over Vega, Applicant' arguments have been fully considered but are deemed not persuasive.

Vega teaches a method of gene therapy based on the use of homologous recombination using linear double stranded or single stranded DNA, fragments derived from genomic DNA covering the mutation in a particular gene. Although the fragment need only cover the-mutation and have flanking sequences homologous to the targeted DNA, it can encompass the whole gene, for instance to correct regulatory defects in unexpressed sequence. As a consequence, the replacement fragment may comprise at least one exon and 5' and 3' flanking intronic sequences. The replacement fragment may be associated with recombination active proteins to improve efficiency of targeting. Delivery means taught include microinjection. Ex vivo and in vivo approaches are taught.

Applicant argues that their claims exclude foreign genes. The claims as written do not exclude foreign genes. The method's intent is to replace a target fragment; the limitation recited for the replacement DNA fragment does not exclude a foreign gene since it could be located between two replacement fragments and the intent of the method would be achieved. If no foreign gene or fragment may be included, this should be recited in the claim. With regard to Vega, the replacement DNA consists of a "fragment of DNA without sequence foreign to the target locus, containing the correct version of the mutation at the locus as the only source of non-homology" (p. 246, column bridge). Vega therefore does not teach the use of vector sequences in the replacement DNA. Vega also teaches the same gene. The rejection over Vega is extended to new claims 41-44 as teaches the use of human cells (see entire article).

Art Unit: 1636

6. With regard to the rejection of claims 17, 20, 21, 23, 27-30, 32, 37, 41 and 42 under 35 U.S.C. §102(b) as being anticipated by Shesely et al (Proc. Natl. Acad. Sci. USA (1991) 88:4294-4298), Applicant provided no arguments in the after final submission filed 3 December 2001. The rejection is therefore maintained.

7. With regard to the rejection of claims 17, 18, 20-22, 27-32, 37-39, and 41-44 stand rejected under 35 U.S.C. §102(e) as being anticipated by Kay et al (USP 5,612,205), Applicant' arguments have been fully considered but are deemed not persuasive.

Kay et al teach a method of homologous recombination in mammalian cells comprising the use of at least two fragments derived from genomic DNA sequence each having a region of homology with the other and which are co-transfected into the target cell. The at least two fragments recombine homologously to form a single DNA fragment which may then homologously recombine with the genomic target sequence. In Example 1, three fragments, each comprising at least one exon and flanking 5' and 3' intronic sequences, are microinjected into male pronuclei of fertilized mouse eggs wherein the three fragments homologously recombined with each other and with the endogenous albumin gene. Southern hybridization was used to assess the homologous recombination. The method may be used in ex vivo gene therapy approaches to correct genetic diseases due to mutant cystic fibrosis or β hemoglobin genes. The method must be used in recombination competent cells, that is, cells containing recombinases, endogenous or otherwise. See entire document, especially col. 3, lines 12-16, col. 6, lines 55-67, col.8, lines 6-56, col. 10, lines 10-11. and col. 12, line 5- col. 13, line 6.

Applicant argues that the teachings of Kay involve the use of plasmids containing 50 kb pieces of DNA that include substantial nonhomologous regions. This is not persuasive because while Kay et al propagate their replacement DNA sequence in a vector, all of the plasmid sequence is removed by restriction enzyme digestion prior to carrying out the method of target replacement. See col.12, lines 50-52. Thus, Kay et al does not teach vector sequence and therefore still anticipates the claims. The size of the fragment used is not relevant as the claims do not recite a size limitation. The rejection over Kay is extended to new claims 41-44 as Kay teaches the use of murine and human cells (see entire document).

8. With regard to the rejection of claim 37 stands rejected under 35 U.S.C. §102(b) as being anticipated by Tsui et al (WO 91/10734), Applicant' arguments have been fully considered but are deemed not persuasive.

Tsui et al teach generating specific exons from the cystic fibrosis gene using PCR and primers that anneal to the flanking intronic sequences. The result from such a PCR reaction is an aqueous composition comprising a DNA fragment comprising an exon with flanking 3' and 5' intronic sequences which are homologous to the specific corresponding intron sequences in the cystic fibrosis gene. See Figure 18 and pp. 64-66.

Applicant argues that Tsui merely discloses a number of specific mutations that give rise to cystic fibrosis and does not teach or suggest how to correct such a mutation or a composition comprising a replacement DNA fragment and a delivery vehicle. Applicant is reminded that the intended use is given no patentable weight. Thus,

Art Unit: 1636

although Tsui does not teach using their PCR-generated fragments of the cystic fibrosis gene, these fragments do have all the limitations recited in claim 37 (contrary to Applicant's assertion) and thus anticipates claim 37. See Figures 18 (drawing sheets 30-43), 19 and pp. 64-65.

Conclusion

Claims 17-44 are rejected.

All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Art Unit: 1636

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 11:00 AM to 7:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, can be reached on (703) 305-1998.

The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

March 10, 2003



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